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Review

Sexual differentiation of the human brain: Relation to gender identity, sexual orientation and neuropsychiatric disorders

Ai-Min Bao [a,*], Dick F. Swaab [b]

[a] Department of Neurobiology, Key Laboratory of Medical Neurobiology of Ministry of Health of China, Zhejiang Province Key Laboratory of Neurobiology, Zhejiang University School of Medicine, Hangzhou, China
[b] Netherlands Institute for Neuroscience, Institute of the Royal Netherlands Academy of Arts and Sciences, Amsterdam, The Netherlands

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ABSTRACT

During the intrauterine period a testosterone surge masculinizes the fetal brain, whereas the absence of such a surge results in a feminine brain. As sexual differentiation of the brain takes place at a much later stage in development than sexual differentiation of the genitals, these two processes can be influenced independently of each other. Sex differences in cognition, gender identity (an individual's perception of their own sexual identity), sexual orientation (heterosexuality, homosexuality or bisexuality), and the risks of developing neuropsychiatric disorders are programmed into our brain during early development. There is no evidence that one's postnatal social environment plays a crucial role in gender identity or sexual orientation. We discuss the relationships between structural and functional sex differences of various brain areas and the way they change along with any changes in the supply of sex hormones on the one hand and sex differences in behavior in health and disease on the other.

1. Introduction

From the first days after birth sex differences are already expressed in human behavior. For example, on their first day of life, female neonates prefer looking at human faces while male infants look more at mechanical mobiles [30]. From the age of 3–8 months, girls were found to choose dolls over the toy-cars and balls that boys prefer [2]. The toy-preference behavior cannot be explained by social pressure, because when dolls, toy-cars and balls were offered to green vervet monkeys, the females consistently chose the dolls and showed anogenital sniffing, while the males preferred the toy-cars and balls [1,58,61,137,141]. It is of interest to note that girls with congenital adrenal hyperplasia (CAH), meaning they were exposed to high testosterone levels in the womb, tend to choose boys as playmates, prefer boys' toys and exhibit some male-typical personality features [94,80], a strong indication of the crucial role that testosterone levels play during pregnancy with regard to the development of such sex differences in behaviors. It is thus logical to propose that the sex differences in playing behavior originated in evolution before the hominids, and are imprinted under the influence of testosterone during our intrauterine development. A similar sex difference is seen in children's spontaneous drawings. Girls of 5–6 years old tend to draw women, flowers and butterflies in bright colors, while boys prefer to draw more technical objects – soldiers and fighting, and means of transportation, in bird's-eye view compositions and using darker colors. Girls who had CAH showed male drawing characteristics, even if the CAH was treated immediately after birth [65]. Apparently fetal exposure to higher levels of male hormones has lasting effects on playing behavior and artistic expression.

Atypical toy preference does, however, not necessarily prognosticate a gender-identity disorder in adulthood. Rather, it is predictive of homosexuality [138]. Aggressive behavior in adulthood has also been related to prenatal testosterone levels in men [82]. In addition, sex differences play a role in the risk of contracting neuropsychiatric disorders such as depression, anxiety, schizophrenia, drug abuse, and Alzheimer's disease (AD) (Table 1). We will introduce neuroendocrine mechanisms involved in such sex differences.

2. Organizational effects of sex hormones during early development and activational effects of sex hormones later

The fetal gonads develop under the influence of a cascade of genes, which in boys begins with the sex-determining gene on the Y-chromosome (*SRY*) [93]. The production of testosterone and the peripheral conversion of testosterone into dihydrotestosterone between weeks 6 and 12 of pregnancy are essential for the formation of a boy's penis, prostate and scrotum. However, the development of the female sexual organs in the womb is

* Corresponding author.
E-mail address: baoaimin@zju.edu.cn (A.-M. Bao).

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Table 1
Ratios for women over men suffering from a selection of neurological or psychiatric diseases (for references see [116]).

Disease	Women:men (%)
Rett syndrome	100:0
Postoperative hyponatremic encephalopathy with permanent damage or death	96:4
Anorexia nervosa	93:7
Lymphocytic hypophysitis	90:10
True (central) precocious puberty	90:10
Hypnic headache syndrome	84:16
Bulimia	75:25
Alzheimer's disease	74:26
Multiple sclerosis	67:33
Anxiety disorder	67:33
Anencephaly	67:33
Posttraumatic stress disorders	70:30
Dementia	64:36
Unipolar depression, dysthymia	63:37
Whiplash	60:40
Severe learning disability	38:62
Substance abuse	34:66
Amyotropic lateral sclerosis	33:67
Stuttering	29:71
Schizophrenia	27:73
REM sleep behavioral disorder	24:76
Male-to-female vs. female-to-male transsexuals	28:72
Dyslexia	23:77
ADHD	20:80
Autism	20:80
Sleep apnea	18:82
Kallmann syndrome	17:83
REM sleep disorder	13:87
Gilles de la Tourette syndrome	10:90
Kleine–Levin syndrome	0:100

Note: abbreviations: REM = rapid eye movement ; ADHD = attention deficit hyperactivity disorder.

primarily based upon the absence of androgens. Once the differentiation of these sexual organs is settled, sexual differentiation of the brain happens, by permanent *organizing effects* of sex hormones on the developing brain [117]. During puberty, the brain circuits that have been organized in the womb will be *activated* by sex hormones.

The main mechanism responsible for gender identity and sexual orientation involves a direct effect of testosterone on the developing human brain, as shown in different disorders. Complete androgen insensitivity syndrome (CAIS) is caused by different mutations in the gene for the androgen receptor (AR). Affected XY-males develop as phenotypical women and experience 'heterosexual' orientation and fantasies without gender problems [142]. When a male fetus has a deficiency of 5α-reductase-2 or 17β-hydroxy-steroid dehydrogenase-3, preventing peripheral testosterone from being transformed into dihydrotestosterone, a 'girl' with a large clitoris will be born. These XY-children are generally raised as girls. However, when testosterone production increases during puberty, the 'clitoris' grows to penis size, testicles descend, the children's build begins to masculinize and becomes more muscular. Despite the fact that these children are initially raised as girls, the majority (60%) will eventually choose to live as heterosexual males, apparently due to the *organizing* effect of testosterone on early brain development and the *activating* effect of testosterone in puberty (for references see [117,120]. Boys who are born with a cloacal exstrophy, i.e. with bladder exstrophy and a partly or wholly absent penis, are usually changed into girls immediately after birth. A survey showed that only 65% of these children who were changed into girls continued to live as girls once they had reached adulthood. Moreover, when individuals with gender dysphoria were excluded, this figure dropped to 47% [100,85]. These examples show that a direct effect of testosterone on a developing boys' brain and a lack of such an effect on a developing girls' brain are crucial for the development of gender identity and sexual orientation.

It should be noted, however, that although sex hormones are very important for gender identity and sexual orientation, sexual differentiation of the brain is not caused by hormones alone. Genes, too, play a key role in it, with *SRY* and *ZRY* as the possible candidates for this action since they are expressed up to very advanced ages in the human brain, even though strictly speaking the role of these genes in sexual differentiation stops during development [117,18,81]. In addition, it has been found that 50 genes are expressed at different levels in the brains of male and female mouse fetuses, even before the hormones come into play [35]. Moreover, epigenetic changes such as the acetylation and methylation of multiple proteins recruited by sex hormone receptor function are important for the developing nervous system as they affect adult sex differences in rodent brain and behavior [83]. Epigenetic changes are found in the germline – and are therefore inherited – and in somatic cells and generally persist only for one lifetime and are largely context-dependent [32]. The context may be variables such as steroid hormones or endocrine-disrupting chemicals [55], experiences as far-reaching as early child abuse [84], or events as mild as context-dependent learning [77]. Recent evidence shows that AR and estrogen receptors (ERs) interact with histone modifying enzymes, which are associated with neural sexual differentiation [131]. Circulating testosterone activates AR and is converted into estrogen in the brain via aromatase. Extensive sexual dimorphism in the number and projections of aromatase-expressing neurons have been demonstrated and the masculinization of these cells was found to occur independent of AR. However, it was possible to induce it in female rodents by either testosterone or estrogen, indicating a role for aromatase in sexual differentiation. It is suggested that aromatase or the aromatization of testosterone into estrogen is important in activating rat male-specific aggression and urine marking behavior, i.e. the development and activation of neural circuits that control male territorial behaviors [144].

The two critical periods in human development when testosterone levels are known to be higher in boys than in girls are mid-pregnancy and the first three months after birth [117,41,33,134,62]. These fetal and neonatal peaks of testosterone, together with functional changes in steroid receptors, are thought to program to a major degree the development of structures and circuits in a boy's brain for the rest of his life. As sexual differentiation of the genitals takes places much earlier in development (i.e. in the first 2 months of pregnancy) than sexual differentiation of the brain (the second half of pregnancy), these two processes may be influenced independently. In rare cases, this may result in transsexuality, i.e. people with male sex organs who nevertheless have a female identity, or vice versa. It also means that in the event of an ambiguous sex organ at birth, the degree of masculinization of the genitals may not always reflect the degree of masculinization of the brain [117]. Structural differences in the brain resulting from the interaction of genes, sex hormones, and developing brain cells are thought to be the basis of, e.g., sex differences in gender role (behaving as a man or a woman in society), gender identity (the conviction that one belongs to the male or female gender) and sexual orientation (heterosexuality, homosexuality or bisexuality). Factors that interfere with the interactions between sex hormones and the developing fetal brain may permanently influence these behaviors as well as generate the risk of neuropsychiatric disorders (see Section 4).

3. Gender identity and sexual orientation in relation to sex differences in the brain

A sex difference in brain weight is already present in allometric relation to bodysize from the age of 2 years [121]. Structural sex

differences – from the macroscopic to the ultramicroscopic level – have also been observed in the adult brain [116], together with a large number of functional sex differences in a variety of brain regions [120]. Our group was the first to find a structural sex difference in the hypothalamus, more precisely in the sexually dimorphic nucleus of the preoptic area (SDN-POA) [119], later also called the interstitial nucleus of the anterior hypothalamus-1 (INAH1) [4], or the intermediate nucleus (InM) of the human hypothalamus [70].

The SDN-POA of men was found to be 2.5 times larger and to contain 2.2 times more cells than that of women [119] (Fig. 1). These sex differences develop only after the age of 5 and disappear temporarily after the age of 50, then they return after the age of 75 [119,63,125,122] (Fig. 2). Allen et al. described two other cell groups, INAH-2 and INAH-3 that showed larger volumes in men compared to women (2.8 and 2 times larger, respectively) [4]. Moreover, a sex difference was found in the volume and neuron number of the INAH3, but not in the INAH4 [43] (Fig. 3), which was in full accordance with previous data [4,75,22,23]. Other structural sex differences have been found in, e.g., the human anterior commissure, the interthalamic adhesion, the corpora mamillaria [116,3], and the cortex [48].

3.1. Programmed gender identity is irreversible

In the 1960s and 1970s the general assumption was that a child is born as a *tabula rasa* and is subsequently forced into the male or female direction by the convention of society. A clear example is Money's statement [90] that 'Gender identity is sufficiently incompletely differentiated at birth as to permit successful assignment of a genetic male as a girl. Gender identity then differentiates in keeping with the experiences of rearing''. Money also believed that gender imprinting does not start until the age of 1 year, and that its development is well advanced by the age of 3–4 years [90,91]. His view had devastating results in the case of David Reimer, i.e. the John–Joan–John case, in which, based upon Money's view, an 8-month-old boy, who lost his penis due to a mistake during a minor surgical procedure (correcting a phimosis), was made into a girl. The child's testicles were removed before he reached the age of 17 months in order to facilitate feminization. He was dressed in girl's clothes, received psychological counseling and was given estrogens in puberty [29]. According to Money, this child developed as a normal female. However, it later ensued that Reimer never identified as female, and that he in fact resumed his life as a male when he was 14 years old [36]. Unfortunately, years of severe depression, financial instability, and a dissolving marriage led to Reimer's suicide in 2004. This story illustrates the strength of the irreversible programming influence during the intrauterine period on gender identity. There are also other cases describing the results of enzymatic disorders or of cloacal exstrophy that support the existence of early permanent programming of gender identity in the brain by biological factors, such as intrauterine androgen exposure, rather than by social environment and learning (for references see [10,120]).

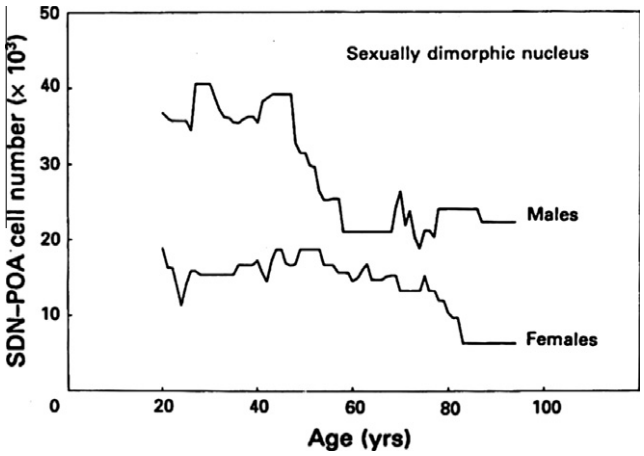

Fig. 2. Age-related changes in the total cell number of the sexually dimorphic nucleus of the preoptic area (SDN-POA) in human hypothalamus. Brains from 30 human subjects (13 males and 17 females), ranging in age from 10 to 93 years of age, without a neurological or psychiatric disorder, were obtained by autopsy. Volume and cell density measurements were made on serial hypothalamic sections (6 μm), and were used to calculate the total number of cells (for details see [63,124]). The general trend in the data is enhanced by smoothing the data points using polynomial regression and a scatter plot smoothing procedure with an equally weighed moving average. Note that in males SDN cell number steeply declines between the ages of 50–70 years, whereas in females a more gradual cell loss is observed around the age of 80 years. These curves demonstrate that the reduction in cell number in the human SDN in the course of aging is a nonlinear, sex-dependent process. (From [63], Fig. 5, with permission).

3.2. Brain development and transsexuality

The most extreme gender-identity disorder is transsexuality. It consists of the unshakeable conviction of belonging to the opposite gender, which tends eventually to lead to a request for hormonal treatment and sex-reassignment surgery [28]. There is no indication of postnatal social factors being responsible for this disorder. On the other hand, only 23% of childhood gender problem cases will lead to transsexuality in adulthood [31]. A number of factors have been found that count as risks for transsexuality (see Table 2, for references see [120], including chromosomal abnormalities, polymorphisms of the genes for ERα, ERβ, AR, and aromatase or

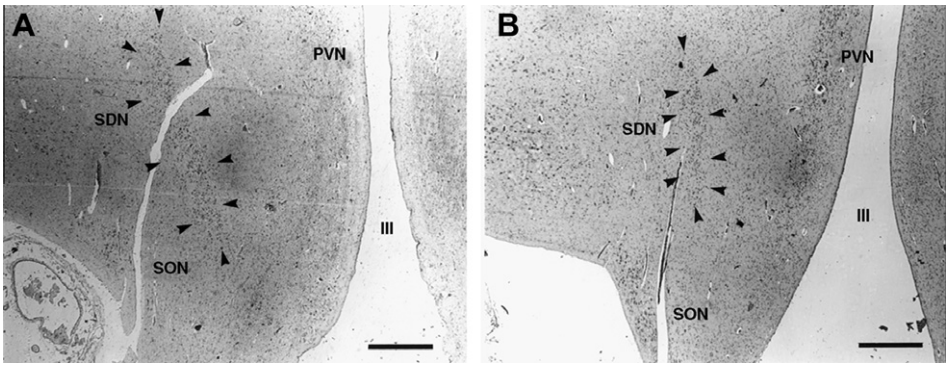

Fig. 1. Thioine-stained frontal section (6 μm) of the hypothalamus of (A) a 28-year-old man and (B) a 10-year-old girl. Arrows show the extent of the sexually dimorphic nucleus of the preoptic area (SDN-POA = INAH-1 = ImN). Note that the male SDN is larger than that of the female. Bar represents 1 mm. (From [124], Fig. 2, with permission).

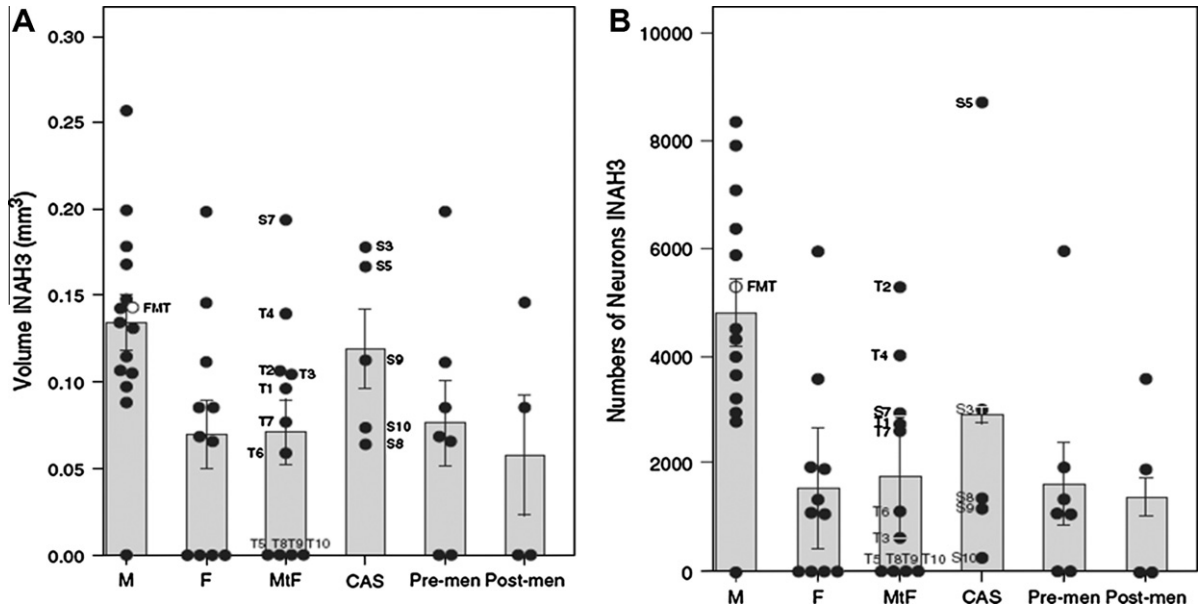

Fig. 3. (A) The interstitial nucleus of the anterior hypothalamus (INAH)-3 volume in thionin staining in different groups, according to their gender identity and hormonal changes in adulthood. M: control-male-group; F: control female group; MtF: male-to-female transsexual group (the individuals are designated as T with a number); CAS: castrated-male-group (the individuals are designated as S with a number); Pre-men: pre-menopausal women; Post-men: post-menopausal women. Bars represent means and standard errors of the mean (SEM). MtF and F groups were statistically different compared to the M group ($P < 0.018$ and $P < 0.013$, respectively). Hormonal changes in adulthood (CAS versus M and Pre-men versus Post-men groups) showed no difference in INAH3 volume. Note that the volume of the female-to-male transsexual subject (FMT, in the M group, 51 years old) is in the male range. Note also that in a considerable proportion of the females (F) and MtF individuals the INAH-3 is small or absent. A gender dysphoric male-to-female patient who was not treated in any way (S7, put in the MtF group, 84 years old) showed a male value for INAH3 volume. (B) Distribution of the INAH3 number of neurons among different groups. Statistically differences were found between men (M) and women (F) ($P < 0.029$) and between men (M) and MtF transsexual groups ($P < 0.002$). The female-to-male transsexual subject (FMT, in the M group, 51 years old) had a masculine INAH3 number of neurons, while the gender dysphoric non-treated patient (S7, put in the MtF group, 84 years old) had a similar number of neurons to the other transsexuals examined. (From [43], Figs. 5 and 6, with permission.)

Table 2
Prenatal factors that influence gender identity that may result in transsexuality (for references see [120]).

Genetic factors
– Twin studies
– Rare chromosomal disorders
– Polymorphisms in ERβ, androgen receptor and aromatase genes
Hormones
– Phenobarbital/diphantoin taken by pregnant mother
– Cloacal exstrophy
– 5 α-reductase-2 or 17β-hydroxy-steroid-dehydrogenase-3 deficiency
– Girls with CAH
– Complete androgen insensitivity syndrome results in XY heterosexual females with female gender identity
Immunological mechanism?
– Fraternal birth order effect
Social factors?
– Postnatal no evidence

Note: abbreviations: CAH = congenital adrenal hyperplasia; DES = diethylstilbestrol.

cytochrome P450 (CYP)-17. Abnormal hormone levels during early development may also play a role, as girls with CAH run an increased risk of becoming transsexual. It should be noted that although the likelihood of transsexuality developing in CAH cases is 100–300 times higher than normal, the risk for transsexuality in CAH is still only 1–3%, whereas the probability of serious gender problems in this group is 5.2%. The consensus is, therefore, that girls with CAH should be raised as girls, even if their genitals are masculinized. Phenobarbital or diphantoin given to pregnant women also presents an increased risk of giving birth to a transsexual child. Both these chemicals may change the metabolism of the sex hormones and may thus act on the sexual differentiation of the child's brain [34]. Furthermore, homosexual male-to-female transsexual people were found to have a later birth order and more brothers than sisters [51], suggesting the presence of immunological processes during pregnancy, directed towards products of the Y-chromosome.

The theory of the origin of transsexuality is based on the fact that the differentiation of sexual organs appears well before the sexual differentiation of the brain. As the two processes are not synchronous, it could be that they take different routes. If this is the case, one might expect to find, in transsexuals, female sexual organs and male brain structures or vice versa. Indeed, we found several reversals, i.e. in the central nucleus of the human bed nucleus of the stria terminalis (BSTc) and in the INAH3, two brain structures from which homologues are also involved in sexual behavior in rodents.

In men the BSTc volume was twice as large as in women and contained twice as many somatostatin neurons [146,72] (Fig. 4). The same was true for the INAH3, found to be 1.9 times larger in men than in women and to contain 2.3 times more neurons [43] (Fig. 3). In addition, a female INAH3 and BSTc have been found in MtF transsexual persons. The only female-to-male (FtM) transsexual person available to us for study so far had a BSTc and INAH3 with clear male characteristics (Figs 3 and 4). These sex reversals were found not to be influenced by circulating hormone levels in adulthood, and seem thus to have arisen during development [43,146,72]. A functional imaging study found, in addition, that pheromones caused a sex-atypical hypothalamic activation in MtF transsexuals [14]. All observations that support the neurobiological theory about the origin of transsexuality, i.e. that it is the sizes, the neuron numbers, and the functions and connectivity of brain structures, not the sex of their sexual organs, birth certificates or passports, that match their gender identities.

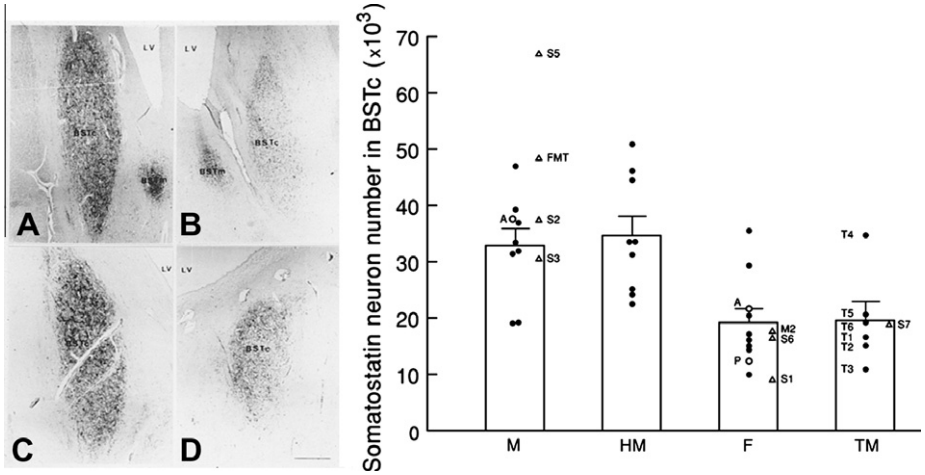

Fig. 4. *Left*: Representative sections of the central nucleus of the bed nucleus of the stria terminalis (BSTc) innervated by vasoactive intestinal polypeptide (VIP). A.heterosexual man; B. heterosexual woman; C. homosexual man; D. male-to-female transsexual. Scale bar, 0.5 mm. LV, lateral ventricle. Note there are two parts of the BST in A and B: small medial subdivision (BSTm) and large oval-sized central subdivision (BSTc) Note also the sex difference (A vs. B) and the fact that the male-to-female transsexual (D) has a female BSTc in size and type of innervation. (From [146], Fig. 2, with permission.) *Right*: Distribution of the BSTc neuron numbers among the different groups according to sex, sexual orientation and gender identity. M: heterosexual male reference group; HM: homosexual male group; F: female group; TM: male-to-female transsexuals. The sex hormone disorder patients S1–6 and M2 indicate that changes in sex hormone levels in adulthood do not change the neuron numbers of the BSTc. The difference between the M and the TM group ($p < 0.04$) becomes also statistically significant according to the sequential Bonferonni method if S2, S3 and S5 are included in the M group or if S7 is included in the TM group ($p \leqslant 0.01$). Note that the number of neurons of the female-to-male transsexual (FMT) is fully in the male range. Whether the transsexuals were male oriented (T1, T6), female oriented (T2, T3, T5), or both (T4) did not have any relationship with the neuron number of the BSTc. The same holds true for heterosexual and homosexual men. This shows that the BSTc number of somatostatin neurons is not related to sexual orientation. A = AIDS patient. The BSTc number of neurons in the heterosexual man and woman with AIDS remained well within the corresponding reference group, so AIDS did not seem to affect the somatostatin neuron numbers in the BSTc. P = Post-menopausal woman. S1 (♀46 yr of age): adrenal cortex tumor for more than 1 yr, causing high cortisol, androstendione, and testosterone levels. S2 (♀ 31 yr of age): feminizing adrenal tumor that induced high blood levels of estrogens. S3 (♂ 67 yr of age): prostate carcinoma; orchiectomy 3 months before death. S5 (♂ 86 yr of age): prostate carcinoma; prostatectomy; orchiectomy, and antiandrogen treatment for the last 2 yr. S6 (♀ 25 yr of age): Turner syndrome (45, X0; ovarian hypoplasia). M2 (♀ 73 yr of age): post-menopausal status. (From [72], Fig. 1, with permission).

Because the sex difference in the BSTc volume does not become apparent until early adulthood [27], this parameter can unfortunately not be used for early diagnosis of transsexuality.

3.3. The brain and sexual orientation

Sexual orientation refers to the gender (male or female) to which a person is attracted, i.e. to the opposite sex (heterosexual), to the same sex (homosexual), or to both sexes (bisexual). Sexual orientation, too, is determined during early development, under the influence of genetic background and factors that influence the interactions between sex hormones and the developing brain (for references see [120] and becomes overt during puberty under the influence of sex hormones. The apparent impossibility of changing a person's sexual orientation in any way [75] is an important argument against the role of society or environment on the development of homosexuality, and against the view that homosexuality is a *lifestyle choice*.

Twin and family studies indicate that the development of sexual orientation is largely a matter of genetics (>50%) [18,6,76]. It is, however, still unclear exactly which genes play such a role. A number of genetic studies have suggested a maternal transmission, i.e. an X-linked inheritance. The X-chromosome has accumulated genes involved in sex, reproduction and cognition. A meta-analysis of four linkage studies suggested that Xq28 may indeed play an important role in male homosexuality [57]. A different technique also indicated that women with homosexual sons had an extreme skewing of X-inactivation – closely associated with gene silencing by DNA and/or histone methylation – as compared to mothers without gay sons. Although this unusual methylation pattern supports a possible role of the X-chromosome in male homosexuality, its mechanism of action is far from clear [19]. However, given the complexity of the development of sexual orientation it is likely to involve many genes. A genome-wide linkage screening did indeed lead to the identification of a number of chromosomal regions and candidate genes that deserved further investigation [92].

Other developmental factors that influence our sexual orientation are, among other things, abnormal hormone levels – as is apparent from the higher prevalence of bisexual and homosexual girls with CAH [148,87] (Table 3, for references see [120]. Between 1939 and 1960 two million pregnant women in the US and Europe were prescribed diethylstilbestrol (DES), an estrogen-like substance meant to prevent miscarriage. However, it turned out that DES, instead of preventing miscarriage, caused a slightly elevated risk of cervical cancer and also increased the chance of bisexuality or homosexuality in girls [86,37] (controversial view see [129]. For boys, the chances that they will be homosexual increase with the number of their older brothers. This phenomenon is known as the *fraternal birth order effect* and is presumed to be due to the

Table 3
Prenatal factors that may influence sexual orientation (for references see [120]).

Genetic factors
– Twin studies
– Molecular genetics
Hormones
– Girls with CAH
– DES
Chemical factors
– Prenatal exposure to nicotine, amphetamines or thyroid medication
Immune response?
– Homosexual orientation in men is most likely to occur in men with a large number of older brothers
Social factors?
– Stress in the mother during pregnancy.
– Being raised by transsexual or homosexual parents does not affect sexual orientation

Note: abbreviations: CAH = congenital adrenal hyperplasia; DES = diethylstilbestrol.

progressive immunization of some mothers to Y-linked minor histocompatibility antigens by each successive male fetus [17,20]. Prenatal exposure to nicotine, amphetamine, or thyroid-gland hormones increases the chances of having lesbian daughters and a mother's stress during pregnancy increases the chance of giving birth to a homosexual son [38,39]. There is no solid proof that postnatal development plays a role of any importance when it comes to directing sexual orientation. On the contrary: children born after artificial insemination with donor sperm and raised by lesbian couples were heterosexually oriented [56]. Proof for the idea that homosexuality is caused by deficient upbringing, or that it is a lifestyle choice or an effect of social learning is also lacking [75]. Therefore, it is to our opinion totally irrational that some people still forbid their children to play with homosexual friends for fear that homosexuality may be catching or learned.

Both structural and functional brain differences have been described in relation to sexual orientation. The first difference was found in the suprachiasmatic nucleus (SCN), the biological clock, that was twice as large in homosexual as in heterosexual men [123,118]. In 1991, LeVay reported that homosexual men have a smaller volume of INAH-3 [75]. Allen and Gorski reported homosexual men to have a larger anterior commissure compared with heterosexual men [3]. Since this structure is found to be larger in heterosexual women than in heterosexual men, which takes care of the left–right temporal cortex connection, it may be involved in sex differences relating to cognition and language [118]. Recently, Savic and Lindström found a possible relationship between the difference in anterior commissure size and the sex-atypical hemispheric asymmetries observed in homosexual men and women [118,106]. It should be noted that the size or number of neurons in the BSTc in relation to sexual orientation appeared to be similar [146,72] (Fig. 4).

Functional scanning also revealed brain differences in relation to sexual orientation. The hypothalamus of homosexual men appeared less responsive to fluoxetine as that of heterosexual men, indicating different activities of the serotoninergic system [69]. Savic et al. explored the influence of putative pheromones on sexual behavior by means of PET, and putative pheromones excreted in perspiration in concentrations 10 times higher in men than in women. They found that these pheromones stimulated the hypothalamus of heterosexual women and homosexual men in the same way. However, heterosexual men were not stimulated by a male scent, suggesting that pheromones may be a contributing factor in determining our choice of partner [106]. Comparing heterosexual and lesbian women revealed that lesbians reacted to pheromones in a sex-atypical, almost reciprocal, way. Sex-atypical cerebral asymmetry and functional connections were also found in homosexual subjects but it proved impossible to primarily ascribe these to learned effects, which suggested a connection to neurobiological entities [118,106].

4. Sex differences in brain disorders

Sex differences in brain and hormone levels are the structural and functional basis of the – often pronounced – sex differences in the prevalence of neuropsychiatric disorders. For Rett syndrome, lymphocytic hypophysitis, anorexia and bulimia nervosa and hypnic headache syndrome, over 75% of the cases were found in women. For dyslexia, attention deficit hyperactivity disorder, autism, sleep apnea, Gilles de la Tourette syndrome, Kallmann syndrome and Kleine–Levin syndrome it was over 75% men (Table 1, for references see [116]. Sex differences do not only show up in the prevalence of these disorders, but also in their signs, symptoms and course. Not only does schizophrenia occur in men 2.7 times more often than in women, men also have a tendency to have a more severe form of this disorder, with poorer premorbid functioning experience, earlier onset, more negative symptoms and cognitive defects, and a larger number of structural brain abnormalities, such as a more severe enlargement of the lateral ventricles. In addition, male patients suffer more severe relapses and respond less well to neuroleptic medication. Female patients, on the other hand, are prone to suffer from more affective symptoms, auditory hallucinations and persecutory delusions. Also, an interaction with gender was observed in the second trimester of pregnancy, when prenatal exposure to maternal stress was studied as a risk factor for schizophrenia, with male foetuses having a higher risk ratio. Factors that produce normal sexual dimorphism in the brain, particularly in the cortex, may be associated with modulating the insults that produce schizophrenia [49].

Other examples of a sex difference in a neurological disease are those following restricted left-hemisphere lesions, resulting in aphasia in 41% of males and 11% of females, whereas manual apraxia was found in 6% of females and 42% of males. After severe subarachnoid hemorrhage, mortality in women was lower (37%) than in men (53%), while the incidence of a favorable outcome was higher in women (42%) than in men (26%). Female traumatic brain injury patients also had a more favorable predicted outcome than male patients (for references, see [116].

According to some studies, the prevalence of AD is higher in women than in men [74], although some other researchers did not find an association between AD and gender and suggested that the excess number of female AD is due to the longer life expectancy of women [59]. However, what supports the presence of sex differences in AD is the observation of an increased number of nucleus basalis of Meynert neurons in women, with more AD-pathology compared to age-matched men [105], and the association found between AD and a locus on the X-chromosome [147]. Lower endogenous estradiol levels are correlated with poor cognitive, behavioral and functional status in older but non-demented women [40,112], while higher free testosterone levels are associated with better scores on visual and verbal memory, visuospatial functioning, and visuomotor scanning in elderly non-demented men [143,89]. Several studies support the idea of the postmenopausal decrease in estrogen levels being an important factor in triggering the pathogenesis of AD. For instance, women with high serum concentrations of bioavailable estradiol are less likely to develop cognitive impairments than women with low concentrations [66,79,145]. In old men, endogenous testosterone levels are not associated with a risk for cognitive decline and AD. However, higher estrogen levels increase this risk [44]. Cerebrospinal fluid (CSF) levels of estradiol were found to be lower in AD patients than in controls, and within the AD group the estradiol levels are inversely correlated with Aβ-42 concentrations, which has been interpreted as corresponding to the beneficial effects of estrogens on AD [107].

Whether sex differences in the brain that arise in development (*organizing effects*) are indeed the basis for the sex difference in neurological or psychiatric diseases has yet to be established. Alternative mechanisms that may be involved are the immediate effects of differences in circulating sex hormone levels (*activating effects*), caused by sex hormone-stimulated gene transcription, as shown in depression (see below). As far as the close correlation between the stress response and a variety of the neuropsychiatric diseases mentioned above is concerned, elucidating the sex differences in our stress-coping behaviors is of importance.

4.1. Stress-coping behavior: the presence of sex differences

The term 'stress', first used by Selye in the 1930s, refers to the consequences of any human or animal organism failing to respond appropriately to emotional or physical threats, whether imaginary or real [111]. We react to stressors with the stress response – a

rapid, automatic process also known as 'fight-or-flight'. Our stress-coping abilities ensure the continuance of the gene pool and thus the survival of the human race. Animal and human studies have shown that the female brain's innate strategy to handle stress differs from that of the male brain [127,128]. Young human males tend to take more risks in relation to conflicts [24], outdoor activities [64] or when driving a car [26,42] than females do. In addition, men are more likely to show physical aggression. They commit 89% of all murders and 99% of all sexual crimes [114], while women are more likely to engage in acts of indirect aggression: spreading vicious rumors, gossiping, telling others not to associate with an intended victim, or even fabricating stories about that person [115]. Research also indicates that sex differences with respect to indirect aggression are present in children as young as 8 years old, increase through age 15, and seem to persist into adulthood [15,16].

4.2. Sex and age differences in the brain stress-coping system: neurobiology

One of the key systems in the regulation of the stress response is the hypothalamo-pituitary-adrenal (HPA) axis [12]. In brief, the hypothalamus releases corticotropin-releasing hormone (CRH) in response to a stressor, which triggers the pituitary gland to secrete adrenocorticotropin (ACTH) into the bloodstream. It subsequently causes corticosteroid release from the adrenal cortex – mainly cortisol in humans. Cortisol is a major stress hormone that also acts on many other organs and brain circuits, such as the hippocampus, amygdala and prefrontal cortex (PFC), that participate in feedback regulation [101]. After the threat has passed, the stress response is shut down by cortisol, which also exerts a negative feedback effect on the pituitary and hypothalamus in close collaboration with neurotransmitters such as gamma-amino-butyric acid [13,71]. Part of the CRH neurons in the hypothalamic PVN co-express arginine vasopressin (AVP) and when released together into the portal capillaries, AVP strongly potentiates ACTH-releasing activity [45,102]. In addition, circulating AVP from the supraoptic nucleus (SON) may induce ACTH release from the pituitary [47]. Most cellular responses to CRH in the brain are mediated by CRH receptor (CRHR) association with the GTP-binding protein, G(s). Animal studies have found enhanced CRHR-G(s) coupling in cortical tissue of unstressed female rats, while previous stressor exposure abolished this sex difference by increasing CRHR-G(s) coupling selectively in males [7]. In addition, differences in CRHR trafficking were identified that could compromise stress adaptation in females. Specifically, stress-induced CRHR association with beta-arrestin2 – an integral step in receptor internalization – was found exclusively in male rats. These findings indicate that increased cellular signaling and compromised internalization of CRHR function render the female CRH-receptive neurons more sensitive to low levels of CRH and less adaptable to high levels of CRH, which may be one of the mechanisms underlying a female's increased vulnerability to stress-related pathology [7].

Sex differences in stress regulation have important implications for understanding the physiological differences in the male and female brain and their impact on vulnerability in disorders associated with stress. Women are better at expressing emotions [25], tend to score higher on scales related to emotional experiences such as neuroticism [54], and have an increased risk of suffering from depression and most anxiety disorders [140]. Morphometric studies have shown sexual dimorphism in several brain structures, such as the cingulate and ventrolateral prefrontal cortices (larger in women) and the medial temporal structures, including the amygdala (larger in men), to be implicated in emotional processing [48,53,95,99]. These structural differences are hypothesized to be programmed by sex steroids early in development [48].

The HPA-axis activity and autonomic responses tend to be lower in women between puberty and menopause compared to men of the same age [68]. Roca et al. found that, compared with age-matched women, young to middle-aged (18–45 yr) men showed that pharmacological (CRH) or physical (exercise) stressors resulted in increased stimulated ACTH and cortisol. This result was obtained in the absence of sex differences in estradiol or testosterone levels, as the subjects underwent gonadal suppression with the GnRH agonist leuprolide acetate at the time of testing [103]. It is thus based upon an organizing rather than an activating effect of sex hormones. In addition, the secretion of cortisol after exercise and the initial secretion (0–30 min) of ACTH to either of the stressors are significantly larger in this group of men than in women. It has also been found that in response to psychological stress the HPA-axis is activated to a greater extent in elderly men than in women [130,73,132]. Cortisol production rate is clearly higher in men than in women [136,113]. Our group has found gender differences in the number of CRH-expressing neurons in the human hypothalamic PVN that may be related to this phenomenon. We observed (i) a significant age-related increase of CRH neurons in men, but not in women and (ii) a significantly larger amount of CRH neurons in men than in women (Fig. 5). We also showed that an abnormal hormone status, for instance due to castration or ovariectomy or due to a sex-hormone-producing tumor, was accompanied by changes in CRH neurons number, illustrating that there are also activating effects of sex hormones on CRH neurons (Fig. 6) [8]. The age-related activation of CRH neurons in men can be explained by a number of factors, for instance a decreased function of the hippocampus, which is more sensitive to the process of aging than the PVN and which inhibits the activity of the HPA-axis [46,88]. In this respect, it is of interest that a significant age-related decline of hippocampal volume was found in men but not in women [21,98]. Increasing insensitivity of the feedback of cortisol on the HPA-axis may be another factor involved in the activation of the HPA-axis in men during aging [52]. AVP is also involved in the stress response. Baseline AVP was found to be significantly higher in the elderly than in young men and women [104]. In addition, men have higher

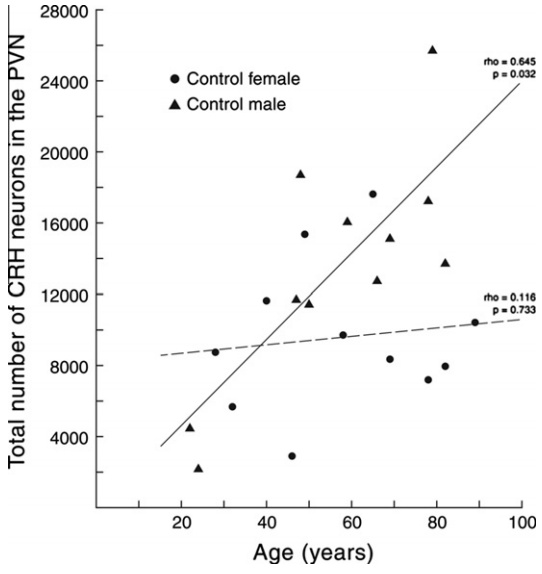

Fig. 5. The total number of corticotropin-releasing hormone (CRH)-immunoreactive neurons in the hypothalamic paraventricular nucleus (PVN) of control males (▲) and females (●). The control males had significantly ($p = 0.004$) more CRH neurons than control females from age 24 onwards and showed a significantly positive correlation (the solid line) between age and total number of CRH neurons. The control female group did not show significant correlation (the dashed line) between age and total number of CRH neurons. (From [8], Fig. 2, with permission.)

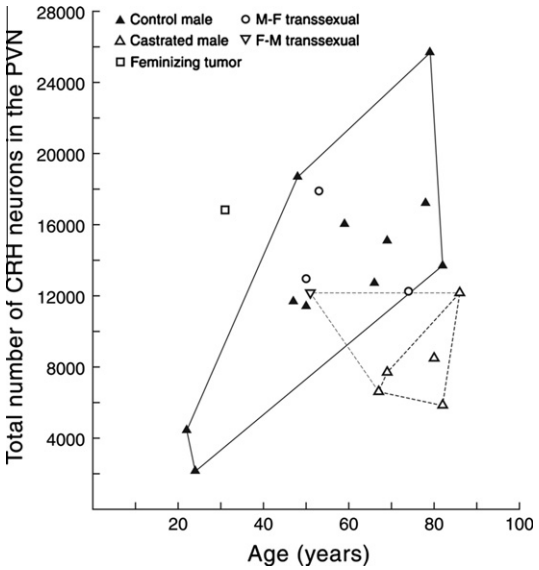

Fig. 6. The total number of corticotropin-releasing hormone (CRH)-immunoreactive neurons in the hypothalamic paraventricular nucleus (PVN) of control males and subjects with abnormal sex hormone status. Values of control-male-group (▲, solid line), castrated-male-group (Δ, dashed line), and 'extended group', i.e. the castrated-male-group (Δ) plus an ovariectomized female-to-male (F–M) transsexual (▽, dashed line), are delineated by a minimum convex polygon, in order to show not only the variability between the patients and the differences between the groups, but also that the increase of CRH-expressing neurons occurs only in men. Note that the total number of CRH neurons in the PVN of the five castrated males ($n = 5$, age $\geqslant 67$) is significantly ($p = 0.008$) lower than that of the matched old control males ($n = 5$, age $\geqslant 66$). Such a significant difference remained ($p = 0.009$) when the ovariectomized F-M transsexual was included in the 'extended group' ($n = 6$, age $\geqslant 51$) compared with the matched control males ($n = 6$, age $\geqslant 50$). The total numbers of CRH neurons in the three M-F castrated-with-estrogen-replacement M-F transsexuals (○) were significantly larger than those in the castration group ($p = 0.036$) and the 'extended group' ($p = 0.024$), while there was no significant difference when compared with age-matched control males (age 50–70, $n = 6$, $p = 0.905$; or age 50–78, $n = 5$, $p = 1.000$). The 31-year-old male with an estrogen-producing adrenal tumor (□) had a very high total number (16,832) of CRH neurons in the PVN. M-F transsexual: male-to-female transsexual; F–M transsexual: female-to-male transsexual; Feminizing tumor: estrogen-producing adrenal tumor. (From [8], Fig. 3, with permission.)

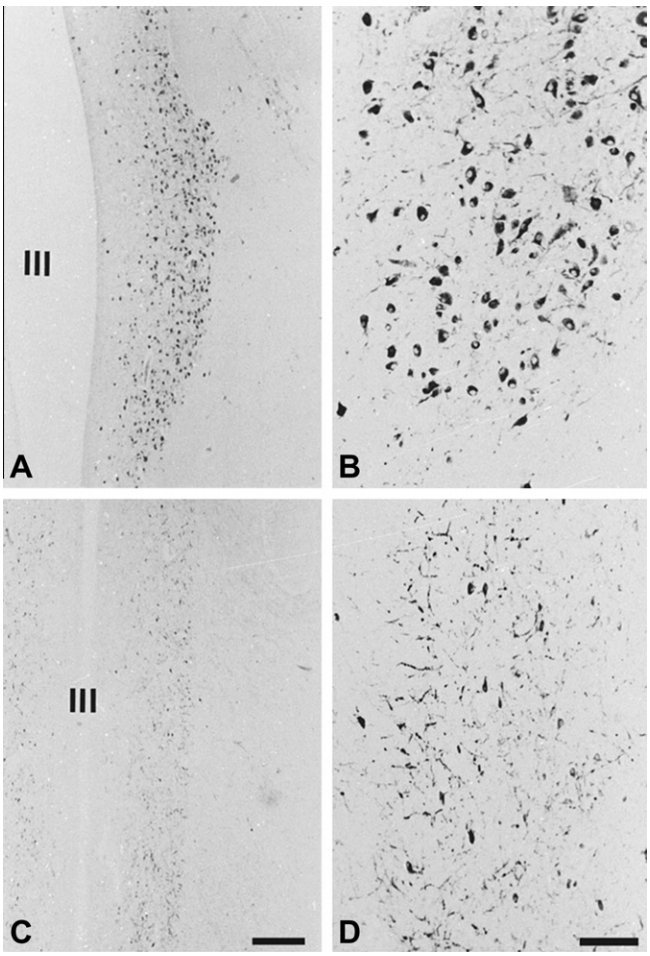

Fig. 8. Immunocytochemical staining of vasopressinergic neurons in the human paraventricular nucleus. Note the difference between a young man (A and B), and a young woman (C and D). Bar: A and C, 400 μm; B and D, 40 μm. (Modified from [67], Fig. 2, with permission.)

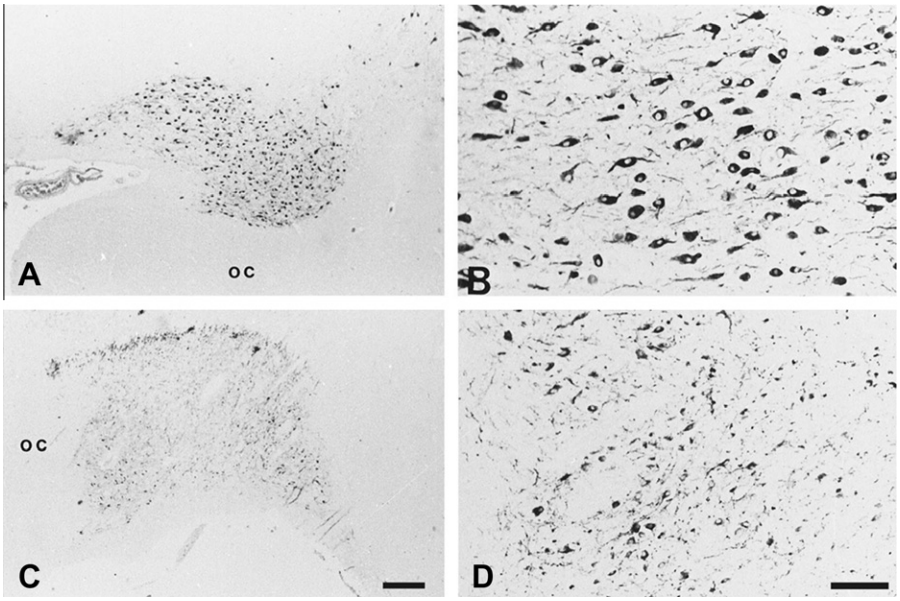

Fig. 7. Immunocytochemical staining of vasopressinergic neurons in the human hypothalamic supraoptic nucleus. Note the difference between a young man (A and B) and a young woman (C and D). Bar: A and C, 400 μm; B and D, 40 μm. (Modified from [67], Fig. 1, with permission.)

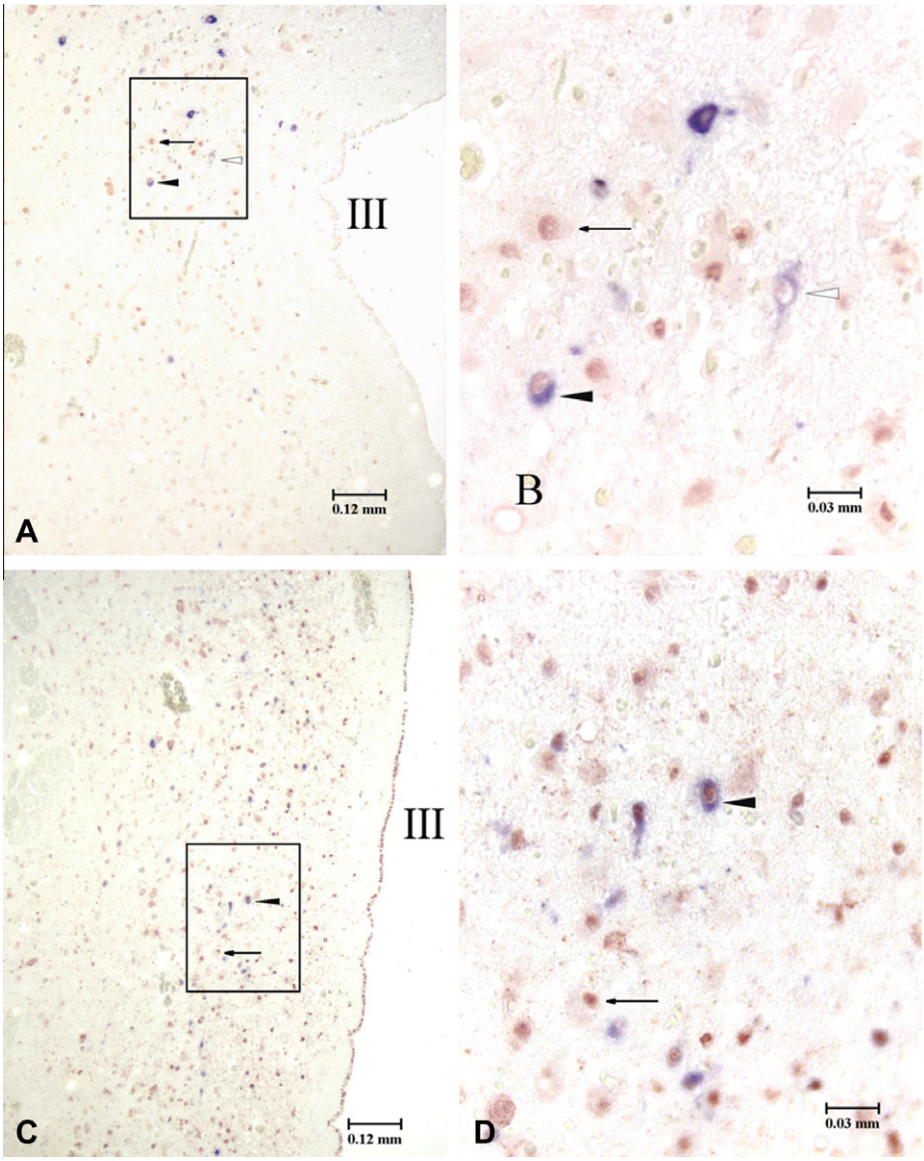

Fig. 9. Frontal section of the PVN in a control (C12) (A and B) and a patient with mood disorder (D10) (C and D) stained for CRH (blue) and ERα (red). (B) and (D) represent a 4× higher magnification of (A) and (C). The arrows and the solid and hollow arrowheads in (A and B) and (C and D) indicate the same place in the preparation to facilitate comparison. Both sections show the central part (mid-level) of the PVN and contain the largest number of stained neurons. It is clear by comparing (A) with (C) and (B) with (D), that the number of stained neurons is markedly increased in this mood disorder patient. III: the third ventricle. The arrow points to an ERα nuclear single-staining cell; the solid arrowhead points to a cytoplasmic CRH-ERα nuclear double-staining cell and the hollow arrowhead points to a CRH single-staining cell. (From [10], Fig. 2, with permission.)

AVP levels than women [135,5]. Sex differences in the size of the AVP neurons, and thus in their function in the human SON (Fig. 7) and PVN (Fig. 8), have also been observed, i.e. the AVP neurons appeared to be larger in young men than in young women (⩽50 yr old), which provide a basis for the reported higher AVP plasma levels in men compared to women [67]. Furthermore, the posterior lobe of the pituitary was found to be larger in boys than in girls [126].

4.3. Sex differences in the prevalence of depression

Sex differences involving the regulation of the activity of the HPA-axis – the 'final common pathway' for a major part of the depressive symptomatology (see [12] and above) – play a role in depression. Unipolar depression and dysthymia are twice as common in women as in men during the females' reproductive years [108,96], something that may, at least partly, be ascribed to the close functional interaction between the HPA and hypothalamo-pituitary-gonad (HPG) axes, and to the fluctuation of circulating sex hormones in women, especially during menstruation, pregnancy, after giving birth, and during the transition of menopause (for references see [12]. Lower testosterone levels were also found in severely depressed [60] and dysthymic male patients [110]. Men who have low total testosterone levels and a shorter CAG codon repeat length in the AR are more likely to suffer from depression [109], while supraphysiological doses of testosterone increased the ratings of manic symptoms in men [97].

The higher prevalence of depression especially during the female's reproductive stages, where fluctuating hormone levels are present, suggests that *fluctuations* in sex hormone levels may play an important role on the vulnerability for mood disorders. In this respect, it is of interest that we found that the amplitudes of diurnal estradiol rhythms were significantly higher in female major depression (MD) patients than in controls [9]. Also, the significant

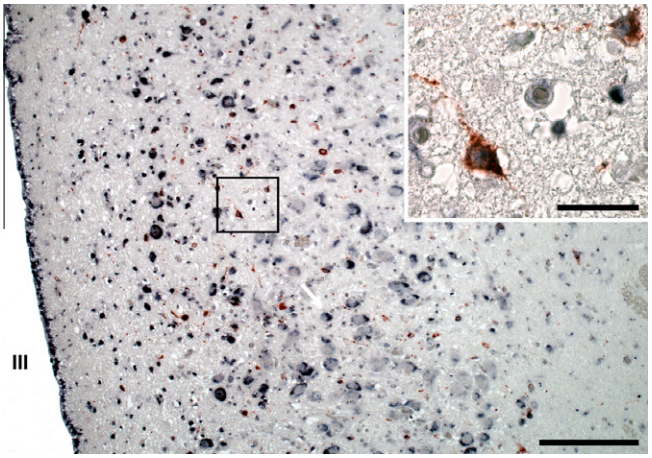

Fig. 10. Frontal section of the paraventricular nucleus in a subject stained for corticotropin-releasing hormone (CRH) (red) and androgen receptor (AR) (blue). III: the third ventricle. The upper-right corner represents a higher magnification of the framed field and shows cytoplasmic CRH (red)–AR (blue) nuclear double-staining neurons. Bar in the upper-right corner = 16 μm; in the lower right corner = 100 μm. (From [11], Fig. 4, with permission.)

differences in the brain stress response circuitry that were observed in different phases of the menstrual cycle indicate that females are endowed with a natural hormonal capacity to regulate the stress response in a way that differs from males [50].

The co-localization of CRH and sex hormone receptors we found point to a direct effect of sex hormones on CRH neurons. Both the nuclear ERα [10] and the nuclear AR [11] are present in CRH-expressing neurons in the human hypothalamic PVN (Figs. 9 and 10). In addition, both males and females showed a closely related up-regulation of CRH and nuclear ERα in mood disorders [10]. The fact that the human CRH gene promoter contains five perfect, half-palindromic estrogen-responsive elements (EREs) is well-known [133]. Animal studies have shown that estrogens stimulate CRH production [78]. In addition, we have identified an androgen-responsive element (ARE) in the CRH gene promoter region that initiates a repressing effect of AR on CRH expression [11], which is in agreement with an animal study showing that androgens inhibit CRH production [78]. Significantly increased CRH-mRNA levels accompanied by a significantly increased expression of ERα-mRNA and significantly decreased expression of AR-mRNA in the PVN of the depressed patients were revealed by laser microdissection plus qPCR technique [139], which not only supported the role of sex hormones, with clear sex differences, in depression, but also raises the possibility that a disturbed balance of the factors that affect CRH activity may contribute to the activation of the HPA-axis. The observation that estrogens stimulate while androgen inhibits CRH transcription goes some way to explain the sex differences seen in the prevalence of MD, a disorder in which the HPA-axis is regarded as the final common pathway for the pathogenesis of depression.

5. Conclusions

During the intrauterine period, gender identity, sexual orientation and other behaviors are programmed in the brain in a sexually dimorphic way. The human fetal brain develops into the male direction through a direct action of testosterone and in the female direction through the absence of such an action. Sexual differentiation of the genitals takes place before the sexual differentiation of the brain. The degree of genital masculinization does thus not necessarily reflect the degree of masculinization of the brain. Also, evidence for an effect of one's social environment after birth on the development of gender identity and sexual orientation is lacking. Structural and functional sex differences of hypothalamic nuclei or other brain areas in relation to gender identity and/or sexual orientation indicate a complex neuronal network involved in various aspects of sexual behavior. Sex differences in the brain help us to understand the nature of sex differences in behavior and neuropsychiatric disorders, which will hopefully help to bring about sex-specific treatments and prevention strategies.

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